Investigating the causal relationship between allergic disease and mental health

Received: 30 April 2021 | Accepted: 6 August 2021

DOI: 10.1111/cea.14010

ORIGINAL ARTICLE

WILEY

Investigating the causal relationship between allergic disease and mental health

Ashley Budu-Aggrey[1,2] | Sally Joyce[2] | Neil M. Davies[1,2,3] | Lavinia Paternoster[1,2] | Marcus R. Munafò[1,4] | Sara J. Brown[5] | Jonathan Evans[2,6] | Hannah M. Sallis[1,2,4,6]

[1]Medical Research Council (MRC) Integrative Epidemiology Unit at the University of Bristol, Bristol, UK

[2]Bristol Medical School, Population Health Sciences, University of Bristol, Bristol, UK

[3]K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

[4]School of Psychological Science, University of Bristol, Bristol, UK

[5]Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, The University of Edinburgh, Edinburgh, UK

[6]Centre for Academic Mental Health, Population Health Sciences, University of Bristol, Bristol, UK

Correspondence
Ashley Budu-Aggrey, Medical Research Council (MRC) Integrative Epidemiology Unit at the University of Bristol, Bristol, UK.
Email: ashley.budu-aggrey@bristol.ac.uk

Funding information
AB-A, ND, LP, MRM and HMS work in a research unit funded by the UK Medical Research Council (MC_UU_00011/1, MC_UU_00011/7). LP received funding from the British Skin Foundation (8010 Innovative Project) and the Academy of Medical Sciences Springboard Award, which is supported by the Wellcome Trust, The Government Department for Business, Energy and Industrial Strategy, the Global Challenges Research Fund and the British Heart Foundation [SBF003\1094]. HMS is supported by the European Research Council (Grant ref: 758813 MHINT). This work was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at the University Hospitals Bristol National Health Service Foundation Trust. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care. SJB holds a Wellcome Trust Senior Research Fellowship in Clinical Science (106865/Z/15/Z) and a British Skin Foundation large project grant. NMD

Abstract

Background: Observational studies have reported an association between allergic disease and mental health, but a causal relationship has not been established. Here, we use Mendelian randomization (MR) to investigate a possible causal relationship between atopic disease and mental health phenotypes.

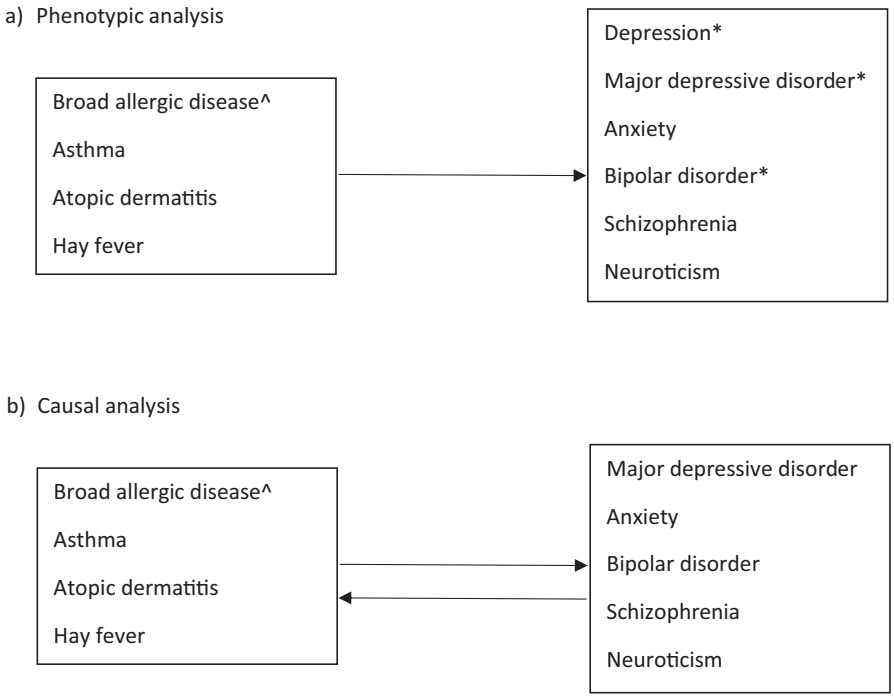
Methods: The observational relationship between allergic disease and mental health was investigated in UK Biobank. The direction of causality was investigated with bi-directional two-sample MR using summary-level data from published genome-wide association studies. A genetic instrument was derived from associated variants for a broad allergic disease phenotype to test for causal relationships with various mental health outcomes. We also investigated whether these relationships were specific to atopic dermatitis (AD), asthma or hayfever. Given the multiple testing burden, we applied a Bonferroni correction to use an individual test *p*-value threshold of .0016 (32 tests).

Results: We found strong evidence of an observational association between the broad allergic disease phenotype and depression ($OR_{self\text{-}report}$=1.45, 95% CI: 1.41–1.50, $p = 3.6 \times 10^{-130}$), anxiety (OR=1.25, 95% CI: 1.18–1.33, $p = 6.5 \times 10^{-13}$), bipolar disorder ($OR_{self\text{-}report}$=1.29, 95% CI: 1.12–1.47, $p = 2.8 \times 10^{-4}$) and neuroticism ($\beta = 0.38$, 95% CI: 0.36–0.41, $p = 6.8 \times 10^{-166}$). Similar associations were found between asthma, AD, hayfever individually with the mental health phenotypes, although the associations between AD and hayfever with bipolar disorder were weaker. There was little evidence of causality in either direction (all *p*-values>.02).

is supported by a Norwegian Research Council Grant number 295989. The funders had no influence on study design, data collection and analysis, decision to publish or preparation of the manuscript

Conclusion: Using MR, we were unable to replicate most of the phenotypic associations between allergic disease and mental health. Any causal effects we detected were considerably attenuated compared with the phenotypic association. This suggests that most comorbidity observed clinically is unlikely to be causal.

KEYWORDS
allergic disease, association, asthma, atopic dermatitis, causal, hayfever, Mendelian randomization, mental health



GRAPHICAL ABSTRACT
We found strong evidence of an observational association between the broad allergic disease phenotype and depression, anxiety, bipolar disorder and neuroticism. Similar associations were found between asthma, AD, hayfever individually with the mental health phenotypes. When using Mendelian randomization to investigate causality, we found little evidence of causality in either direction. Mendelian randomization suggests observational associations between allergic disease phenotypes and mental health may be inflated

1 | INTRODUCTION

There is a well-documented relationship between allergic disease (including asthma, atopic dermatitis (AD) and hayfever) and mental health.[1-3] However, it is unclear whether this association is causal, or whether confounding factors, or reverse causality, could explain the observed association. Prevalence of common mental health disorders and allergic disease is increasing.[4] Common mental health disorders such as anxiety and depression are some of the largest contributors to the global burden of disease. Establishing whether there is a causal relationship is therefore important, as this could highlight whether effectively treating allergic disease would lead to a reduction in the burden of mental health issues (or vice versa).

Increased prevalence of disorders such as depression, anxiety, schizophrenia, conduct disorder and autism are observed among individuals with AD, particularly those most severely affected.[5,6] Other studies have found evidence of an association between asthma and hayfever with bipolar disorder, depression and schizophrenia.[7,8]

Key Messages

- Mendelian randomization suggests phenotypic associations between allergic disease and mental health may be inflated
- We did not find evidence of causal effects between allergic disease genetic risk and mental health
- Phenotypic analyses were restricted to older adults so findings may not generalize to younger populations

Several hypotheses have been suggested for a causal role of allergic disease on mental health; these include both psychosocial and biological mechanisms. It is possible that social consequences of allergic disease, such as embarrassment due to visible lesions or itching resulting from AD, or results of sleep deprivation are the driving force behind later mental health issues. An alternative hypothesis is the "inflammatory hypothesis," which suggests that the effects of allergic disease on the immune system (such as disturbances in the inflammatory system or increased levels of inflammatory cytokines) could contribute to the presence of mental health disorders.[9,10]

If these associations reflect a true causal effect of allergic disease on mental health, this could suggest targets for potential intervention and prevention targets for subsequent mental health problems. For example, screening, monitoring and/or early intervention among allergic disease patients could reduce the risk of later bipolar disorder. If the effects do act via inflammatory mechanisms, then repurposing existing treatments for inflammatory disease could be effective here. Nonsteroidal anti-inflammatory drugs (NSAIDS) have been suggested to be an effective adjunct therapy for bipolar disorder; however, this finding remains inconclusive.[11,12] Studies investigating the progression of disease rather than onset will further inform on the effectiveness of repurposing opportunities to treat current sufferers.[13]

We used data from the UK Biobank (UKB) study to investigate the phenotypic associations between allergic disease and mental health in a population of European ancestry. UKB is a large longitudinal cohort that recruited participants in the UK aged 40 years and above to investigate the contribution of genetics and environment to the development of disease. We also performed two-sample Mendelian randomization (MR) using summary data from relevant genome-wide association studies (GWAS) to investigate the causal nature of these associations. MR enables us to infer causality using observational data. The method uses genetic variants as a proxy for modifiable exposures, and subject to the instrumental variable assumptions holding, should not be subject to the issues affecting conventional observational epidemiology.[14,15] This is based on the assumptions that the instrumental variable is truly associated with the exposure and not associated with confounders, and also has an effect upon the outcome via the exposure and not via alternative pathways.[14]

Disentangling the nature of the relationship between allergic disease and mental health could enable us to focus efforts on improving intervention or prevention strategies. Whether there is a causal effect of allergic disease on mental health, as suggested by previous observational studies, is a critical question for intervening on the initial presentation of allergic disease to improve mental health outcomes of patients.

2 | METHODS

2.1 | Study populations

2.1.1 | Phenotypic association—UK Biobank

Data were available from UKB for individuals aged between 37 and 73 years,[16] including those with asthma, AD, hayfever and the broad allergic disease phenotype (any one of asthma, AD or hayfever) (Table 1). Phenotype data were also available for mental health and personality traits including depression, anxiety, bipolar disorder, schizophrenia and neuroticism. All individuals were of European ethnicity who had provided written informed consent. UKB is approved by the National Health Service National Research Ethics Service (ref 11/NW/0382; UKB application number 9142).

Mental health and personality phenotypes

Self-reported measures of depression, anxiety, bipolar disorder and schizophrenia were derived from responses to the verbal interview conducted at the initial assessment centre. Responses to this interview are recorded in the non-cancer illness item (variable 20002; categories: depression = 1286, anxiety = 1287, bipolar disorder = 1291, schizophrenia = 1289). We also included stricter definitions of major depressive disorder (MDD) and bipolar disorder that were derived from responses to the touchscreen questionnaire at recruitment (variable: 20126). Neuroticism summary scores were based on 12 neurotic behaviour domains (variable:20127). The neuroticism scores and stricter MDD and bipolar definitions were originally derived by Smith et al[17]; full details are included in the Appendix S1.

Allergic disease phenotypes

Asthma, AD and hayfever phenotypes were also derived from the non-cancer illness item collected at the first assessment centre via verbal interview (variable 20002; categories: asthma = 1111, AD = 1452, hayfever = 1387). Participants were designated as controls for the relevant phenotype if they did not report asthma, AD or hayfever based on the non-cancer illness item, *and* if they did not report a doctor diagnosis of asthma or AD/hayfever as part of the touchscreen questionnaire (variable: 6152). When screening the controls for AD and hayfever, it was not possible to tease these disorders apart using the touchscreen questionnaire so individuals answering yes to this question were excluded from both the AD and hayfever controls. A broad allergic disease phenotype was derived from these phenotypes, participants reporting either asthma, hayfever or AD (or any combination of these phenotypes)

TABLE 1 Descriptive statistics of UK Biobank individuals with allergic disease

Trait	Cases / controls (prevalence)	N
Allergic disease (broad phenotype)	78,768/369,866 (17.6%)	448,634
Asthma	53,031/398,301 (11.8%)	451,332
Atopic Dermatitis	11,571/441,038 (2.6%)	452,609
Hayfever	25,471/427,220 (5.6%)	452,691

were assigned case status. Participants who did not report either asthma, AD or hayfever as described for the individual phenotypes were designated as controls.

2.1.2 | Causal relationship—Summary GWAS data

Published summary GWAS results were available for the most recent GWAS for the broad allergic disease phenotype (n = 360,868), which had considered the existence of any one of the atopic triad (asthma, AD and hayfever)[18] and identified 89 independent ($r^2 < 0.01$) single nucleotide polymorphisms (SNPs) at $p < 5 \times 10^{-8}$. Summary GWAS results were also available for recent large scale GWAS of each of the atopic triad individually, and we used these to identify specific genetic instruments. Independent SNPs ($r^2 < 0.01$) associated at the genome-wide significance threshold were identified for asthma (n = 127,669; 16 SNPs),[19] hayfever (n = 38,838; 37 SNPs)[20] and AD (n = 40,835; 23 SNPs)[21] (Tables S1-S4, S10). Effect sizes for each of these SNPs were extracted from recent GWAS of each mental health phenotype to create our outcome datasets.

Similarly, published GWAS results were available for the mental health outcomes investigated; MDD,[22] bipolar disorder,[23] schizophrenia,[24] neuroticism[25] and anxiety.[26] Genetic instruments were derived from associated independent variants ($p < 5 \times 10^{-8}$; $r^2 < 0.01$) reported for MDD (32 SNPs),[22] bipolar disorder (22 SNPs),[23] anxiety (5 SNPs),[27] schizophrenia (79 SNPs)[24] and neuroticism (66 SNPs)[25] (Tables S5-S9, S10). All published results were from analyses restricted to individuals of European ancestry.

2.2 | Statistical analyses

An overview of the analyses is shown in Figure S1. In brief, we looked at the phenotypic association between broad allergic disease, asthma, AD and hayfever with depression, MDD, anxiety, bipolar disorder, schizophrenia and neuroticism. Bidirectional MR analyses were performed between each of the allergic disease phenotypes and MDD, anxiety, bipolar disorder, schizophrenia and neuroticism.

2.2.1 | Observational analyses

Observational analyses were carried out using individual level data from UKB participants to investigate the phenotypic association between the allergic disease phenotypes and psychiatric traits. This was performed using linear or logistic regression as appropriate while adjusting for age and sex. All observational analyses were performed using Stata 15.[28] Given the multi-testing burden, we note that a global $p = .05$ is equivalent to an individual test p-value of .0016 (32 tests).

2.2.2 | Analysis of causal relationships

MR was then performed using the TwoSample MR R package[29] to determine the causal effect of allergic disease liability upon the risk for mental disorders (Figure 1a). A causal estimate was obtained using the multiplicative random-effects inverse-variance weighted (IVW) method, which is akin to a weighted regression of the SNP-outcome coefficients upon the SNP-exposure coefficients. In doing so, the SNP-exposure and SNP-outcome associations were combined in a meta-analysis. For ease of interpretation, the resulting causal estimates were multiplied by 0.693 to represent the change in outcome per doubling odds of the exposure as demonstrated by Burgess and Labreque.[30]

MR analyses were also performed in the reverse direction to estimate the causal effect of liability for mental health traits upon allergic disease risk (Figure 1b).

2.2.3 | Sample overlap

UKB participants were included in the discovery samples for the broad allergic disease phenotype, hayfever, MDD and anxiety. This sample overlap has the potential to bias causal effect estimates towards the phenotypic exposure-outcome association.[31] To avoid sample overlap, we generated genetic instruments for MDD (Wray et al. 2018) based on summary statistics excluding UKB (31 SNPs). Summary data for hayfever excluding UKB were also available when hayfever was the outcome.[20] An alternative anxiety genetic instrument was also generated using SNP-exposure coefficients from an older anxiety GWAS that did not include UKB.[26] Due to limitations of data availability, there were some analyses where sample overlap could not be avoided, these being when investigating causality between the broad allergic disease and neuroticism (estimated sample overlap =42.0%) and for hayfever and neuroticism (estimated sample overlap =44.4%).

2.2.4 | Sensitivity analyses

The causal estimate could be biased by SNPs within the genetic instrument which act through a horizontally pleiotropic pathway (whereby a SNP affects the outcome by a path other than via the exposure—the bottom dotted arrows in Figure 1). We used four sensitivity methods that rely on different assumptions to test for or account for potential pleiotropy. These are MR-Egger regression,[32] weighted median analysis[32] and the weighted mode-based estimate (MBE)[33] and Cochran's Q statistic.[34] The Steiger directionality test was also performed to ensure the variance explained by the genetic instrument was greater in the exposure compared with the outcome.[35] Where we found evidence of a causal association, we performed a look up of SNPs in the relevant instrument using PhenoScanner[36,37] to identify any that could be associated with pleiotropic traits.

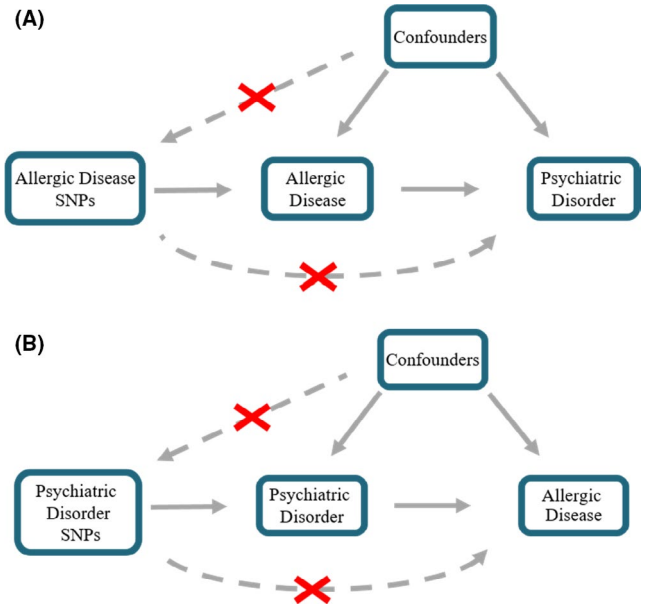


FIGURE 1 Schematic representation of MR analyses. (A) Allergic disease SNPs were used as genetic instruments to investigate the causal effect of allergic disease liability upon various psychiatric disorders and mental health outcomes. (B) SNPs for various psychiatric disorders were used as genetic instrument to investigate to causal effect of liability for psychiatric disorders and mental health outcomes upon allergic disease. SNP = single nucleotide polymorphism

All MR analyses were performed using R (www.r-project.org). The code and datasets used to carry out the MR analyses are available on GitHub (https://github.com/abudu-aggrey/Allergic_Disease_Mental_Health_MR).

3 | RESULTS

3.1 | Observational analyses

We found strong observational evidence for an association of the broad allergic disease phenotype with both self-reported depression (OR=1.45; 95% CI: 1.41–1.50; p-value = 3.63×10^{-130}) and MDD (OR=1.40; 95% CI: 1.35– 1.46; p-value=2.63×10^{-76}) (Figure 2a, Table S11). A strong association was also seen between depression and the individual asthma, AD and hayfever phenotypes, though with different magnitudes (Figure 2a, Table S11). However, we note that adult prevalence of AD (5%–10%),[38] asthma (18.2%)[39] and hayfever (10%–30%)[40] in the population is greater than that identified in UKB (Table 1).

We also found evidence of an association between anxiety and the broad allergic disease phenotype (OR=1.25; 95% CI: 1.18– 1.33; p-value = 6.45×10^{-13}), where stronger evidence was seen with AD and weaker associations with asthma and hayfever (Figure 2a, Table S11). Bipolar disorder was associated with the broad allergic disease phenotype and appeared to be driven by asthma. This association was not consistent for hayfever or AD. (Figure 2a, Table S11). Of the allergic disease phenotypes investigated, only hayfever showed evidence of association with schizophrenia with a protective direction of effect (OR=0.41; 95% CI: 0.23– 0.70; p-value = 1.36×10^{-3}) (Figure 2a, Table S11). All phenotypes showed evidence of association with neuroticism, most strongly with the broad allergic disease phenotype, asthma and AD (Figure 2b, Table S11).

3.2 | MR analyses

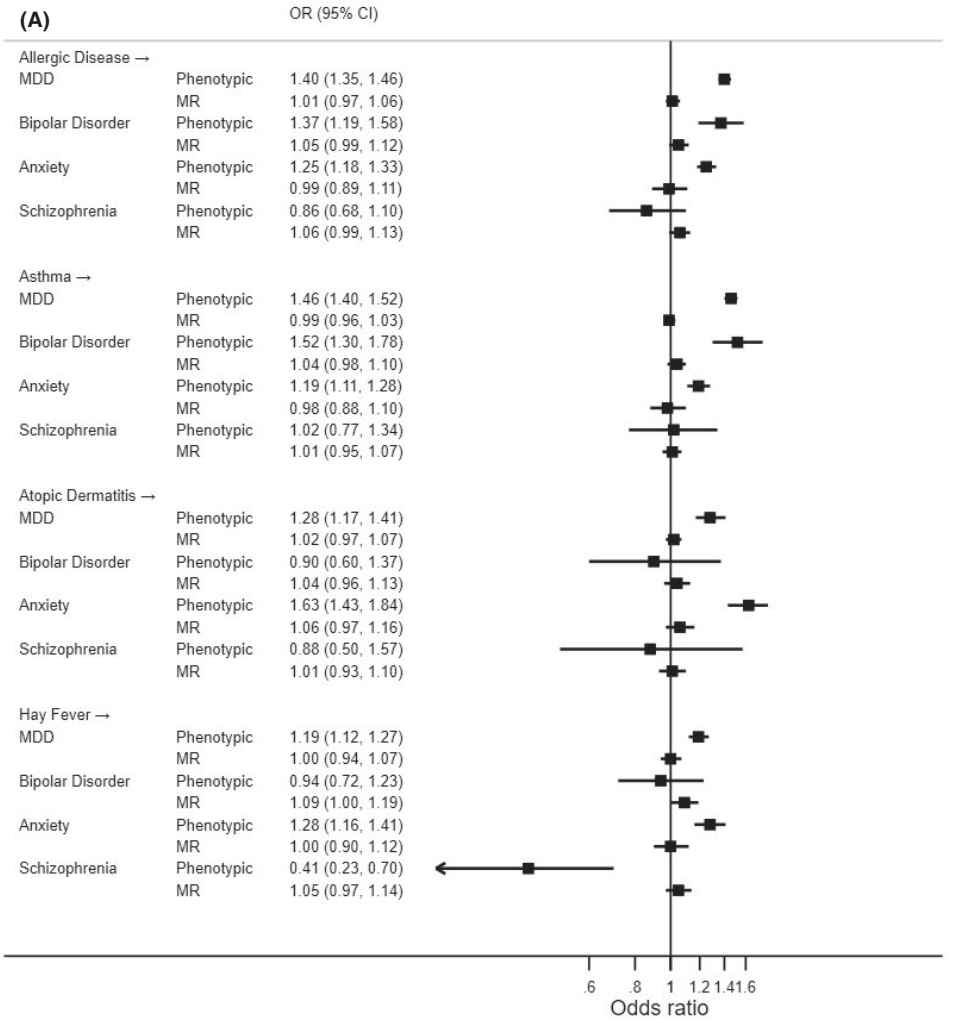
3.2.1 | Causal effect of allergic disease genetic risk upon psychiatric traits—broad phenotype

Two-sample MR found little evidence that genetic liability for the broad allergic disease phenotype causally increases the risk of psychiatric traits (Figure 2a, Table 2, S12). When investigating the causal effect upon MDD risk, the MR estimate was in a consistent direction with that found phenotypically (Figure 2a); however, the phenotypic association failed to replicate in the MR analysis (OR=1.01 per doubling odds of allergic disease; 95% CI: 0.97–1.06; P-value=0.51). These estimates suggest that a reduction in MDD risk >21% or increase in risk MDD >6%, which would be clinically important effects, is unlikely. There was weak evidence that genetic liability for the broad allergic disease phenotype increased the risk bipolar disorder. The direction of effect was consistent with the phenotypic estimate, though the confidence interval crossed the null (OR=1.05; 95% CI: 0.99–1.12; P-value=0.10) (Figure 2a, Table 2, S12), suggesting a reduction in risk >1% or increase >12% is unlikely. The magnitude of effect was also smaller than that found phenotypically.

When looking at the causal effects on anxiety, schizophrenia and neuroticism, the phenotypic association we observed with the broad allergic disease phenotype failed to replicate, and causal effect estimates were null (Figure 2a,b).

3.2.2 | Causal effect of allergic disease genetic risk upon psychiatric traits—individual phenotypes

When assessing individual allergic disease phenotypes, the strongest effect was found between hayfever and increased risk of bipolar disorder (OR=1.09; 95% CI: 1.00–1.19; p-value=0.06) (Table 2, S12, Figure S2) and effect estimates were in a consistent direction across sensitivity analyses. The MR-Egger model suggested a larger effect; however, evidence for this effect was weak (Table S12, Figure S3). No variants were excluded from the hayfever genetic instrument upon Steiger filtering. However, the confidence interval did cross the null and some heterogeneity was detected (Q=65; P-value = 3.69×10^{-04}). There was little evidence of a phenotypic association between hayfever and bipolar disorder, and effects were in opposing directions for self-report and diagnosis. When performing a look up of the hayfever variants in PhenoScanner, there


(A)
OR (95% CI)
Allergic Disease →
MDD Phenotypic 1.40 (1.35, 1.46)
MR 1.01 (0.97, 1.06)
Bipolar Disorder Phenotypic 1.37 (1.19, 1.58)
MR 1.05 (0.99, 1.12)
Anxiety Phenotypic 1.25 (1.18, 1.33)
MR 0.99 (0.89, 1.11)
Schizophrenia Phenotypic 0.86 (0.68, 1.10)
MR 1.06 (0.99, 1.13)
Asthma →
MDD Phenotypic 1.46 (1.40, 1.52)
MR 0.99 (0.96, 1.03)
Bipolar Disorder Phenotypic 1.52 (1.30, 1.78)
MR 1.04 (0.98, 1.10)
Anxiety Phenotypic 1.19 (1.11, 1.28)
MR 0.98 (0.88, 1.10)
Schizophrenia Phenotypic 1.02 (0.77, 1.34)
MR 1.01 (0.95, 1.07)
Atopic Dermatitis →
MDD Phenotypic 1.28 (1.17, 1.41)
MR 1.02 (0.97, 1.07)
Bipolar Disorder Phenotypic 0.90 (0.60, 1.37)
MR 1.04 (0.96, 1.13)
Anxiety Phenotypic 1.63 (1.43, 1.84)
MR 1.06 (0.97, 1.16)
Schizophrenia Phenotypic 0.88 (0.50, 1.57)
MR 1.01 (0.93, 1.10)
Hay Fever →
MDD Phenotypic 1.19 (1.12, 1.27)
MR 1.00 (0.94, 1.07)
Bipolar Disorder Phenotypic 0.94 (0.72, 1.23)
MR 1.09 (1.00, 1.19)
Anxiety Phenotypic 1.28 (1.16, 1.41)
MR 1.00 (0.90, 1.12)
Schizophrenia Phenotypic 0.41 (0.23, 0.70)
MR 1.05 (0.97, 1.14)
.6 .8 1 1.2 1.4 1.6
Odds ratio

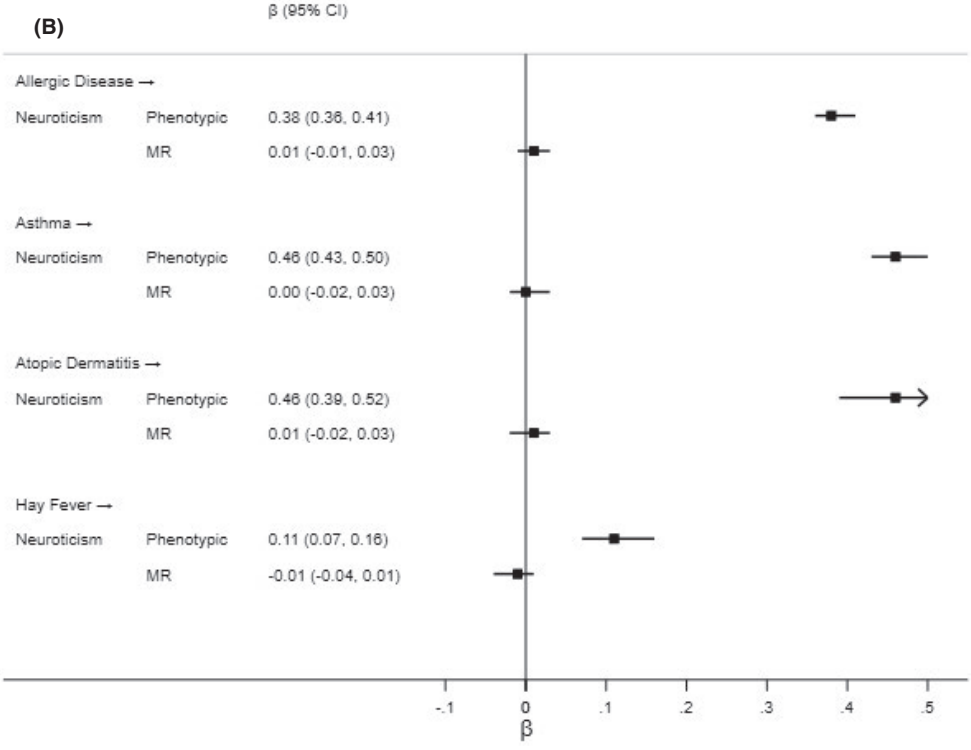

(B)
β (95% CI)
Allergic Disease →
Neuroticism Phenotypic 0.38 (0.36, 0.41)
MR 0.01 (-0.01, 0.03)
Asthma →
Neuroticism Phenotypic 0.46 (0.43, 0.50)
MR 0.00 (-0.02, 0.03)
Atopic Dermatitis →
Neuroticism Phenotypic 0.46 (0.39, 0.52)
MR 0.01 (-0.02, 0.03)
Hay Fever →
Neuroticism Phenotypic 0.11 (0.07, 0.16)
MR -0.01 (-0.04, 0.01)
-.1 0 .1 .2 .3 .4 .5
β

FIGURE 2 Phenotypic association and causal effects of allergic disease on mental health and personality traits. (A) Observational analysis: Estimates (ORs) given for odds of mental health traits in allergic disease sufferers versus non-sufferers. MR Analysis: Estimates are given for odds of mental health outcomes per doubling odds of broad allergic disease phenotype. (B) Observational analysis: Neuroticism estimate (β) given for change in summary score in allergic disease sufferers versus non-sufferers. CI, confidence interval. MR Analysis: Causal estimate given for change in total neuroticism score per doubling odds of broad allergic disease phenotype. CI, confidence interval

TABLE 2 Random-effects IVW MR analyses for causal effect of allergic disease genetic liability on mental health outcomes

Exposure	Outcome	Causal Estimate (95% CI)	*p*-value
Allergic disease	MDD	1.01 (0.97, 1.06)	.51
	Bipolar disorder	1.05 (0.99, 1.12)	.10
	Anxiety	0.99 (0.89, 1.11)	.90
	Schizophrenia	1.06 (0.99, 1.13)	.08
	Neuroticism[a]	0.01 (−0.01, 0.03)	.38
Asthma	MDD	0.99 (0.96, 1.03)	.71
	Bipolar disorder	1.04 (0.98, 1.10)	.19
	Anxiety	0.98 (0.88, 1.10)	.76
	Schizophrenia	1.01 (0.95, 1.07)	.78
	Neuroticism[a]	0.00 (−0.02, 0.03)	.90
Atopic dermatitis	MDD	1.02 (0.97, 1.07)	.50
	Bipolar disorder	1.04 (0.96, 1.13)	.34
	Anxiety	1.06 (0.97, 1.16)	.19
	Schizophrenia	1.01 (0.93, 1.10)	.73
	Neuroticism[a]	0.01 (−0.02, 0.03)	.64
Hayfever	MDD	1.00 (0.94, 1.07)	.98
	Bipolar disorder	1.09 (1.00, 1.19)	.06
	Anxiety	1.00 (0.90, 1.12)	.95
	Schizophrenia	1.05 (0.97, 1.14)	.23
	Neuroticism[a]	−0.01 (−0.04, 0.01)	.22

Note: Estimates given for odds of mental health outcome per doubling odds of allergic disease phenotype.

Abbreviations: CI, confidence interval; MDD, major depressive disorder.

[a]Estimates given for change in total neuroticism score per doubling odds of allergic disease phenotype.

was some evidence of an association with education (Table S14); however, effect estimates were small in comparison with the effect on hayfever so any effects on the MR estimates are likely to be negligible.

Although the strongest phenotypic association was identified between bipolar disorder and asthma, we found little evidence that genetic liability for asthma influenced the risk of bipolar disorder (Figure S4) and the confidence intervals did not overlap with the phenotypic estimates (OR = 1.04; 95% CI: 0.98–1.10; *p*-value = 0.19).

While anxiety and neuroticism were phenotypically associated with asthma, AD and hayfever, there was little evidence that these relationships were causal in the MR analysis. The causal effect estimates were close to the null and were generally not in a consistent direction to the phenotypic estimates (Figures S2, S4-S6).

3.2.3 | Casual effect of psychiatric disorder genetic risk upon allergic disease.

We describe these results in full in the Supplementary Materials (Table S13, Figure S7). In brief, we found little evidence that any of the mental health phenotypes causally affected the broad allergic disease phenotype. The strongest evidence was between MDD and neuroticism genetic risk on the broad allergic disease phenotype; however, the MDD effect estimates were of a smaller magnitude than the phenotypic associations and the confidence intervals did not overlap, while the neuroticism effect estimate was in the opposing direction to the phenotypic association (Table S13, Figures S7-S9).

For the individual allergic disease phenotypes, the strongest evidence was found for bipolar disorder genetic liability having a protective effect upon hayfever (OR = 0.94; 95% CI: 0.90–0.99; *p*-value = 0.02) (Table S13, Figure S10), which is a smaller magnitude of effect than found for hayfever genetic risk upon bipolar disorder. However, a protective effect of bipolar disorder upon hayfever was not observed in the phenotypic analysis.

4 | DISCUSSION

We investigated the association between allergic disease and mental health using both observational regression based on UKB data (a UK longitudinal cohort aged 40 years and over), and two-sample MR approaches based on publicly available GWAS summary data. With the exception of schizophrenia, we found strong evidence of phenotypic associations between all mental health and personality phenotypes investigated with the broad allergic disease phenotype, particularly with

depression, replicating findings previously reported in a Taiwanese population.[3] We also identified associations with specific allergic diseases (hayfever, AD, asthma). Anxiety and neuroticism were phenotypically associated with each of the individual diseases, but the association between the broad allergic disease phenotype and bipolar disorder appeared to be driven by asthma. However, when using an MR approach, we found very little evidence that any of these phenotypic associations were likely to be causal. Where there was evidence for this, the causal effect estimates were of a much smaller magnitude. Given these results, it seems likely that most phenotypic associations between allergic disease and mental health are due to confounding or some other form of bias. This suggests that the observed clinical comorbidity between allergic disease and mental health problems is unlikely to be causal. Therefore, intervening to prevent onset of allergic disease is unlikely to directly improve mental health (and vice versa).

We did find some evidence of a causal effect of genetic liability for bipolar disorder upon hayfever risk. However, we did not find evidence for a phenotypic association. Although evidence for a casual effect of hayfever genetic risk upon bipolar disorder was weak, it is possible that this relationship acts through inflammatory mechanisms. This would support the inflammatory hypothesis, where several psychiatric traits, including bipolar disorder, have been reported to be associated with increased inflammatory markers.[11]

Although our findings suggest there is no direct causal effect of *onset* of allergic disease on the onset of mental health phenotypes, there is some evidence that effectively treating skin disease can improve mental well-being.[41,42] A recent report by the All-Party Parliamentary Group on Skin has recommended that patients with a chronic skin condition should receive an annual assessment of the psychological impact of their condition.[43] In our study, the genetic instruments we used were identified in GWAS which looked at the onset of allergic disease or mental health phenotypes. In primary care and trial settings, interventions often aim to improve these phenotypes rather than prevent their onset, which could have different causal relationships.[13] Methods are currently being developed which will enable us to investigate the causal effects of disease progression rather than disease onset, such as the recent slope hunter approach proposed by Mahmood and colleagues.[44] Future work should follow up these relationships to investigate whether interventions that aim to improve allergic disease show stronger evidence of a causal effect on mental health (and vice versa).

Triangulating findings using both observational and MR approaches using studies with large sample sizes, and across multiple contexts by comparison with published findings from international cohorts, is a particular strength of this study. This enables us to compare the magnitude of effect across approaches. For the majority of our analyses, the confidence intervals for the observational and causal effect estimates did not overlap, indicating that any causal effect of allergic disease is likely to be much smaller than the phenotypic estimates suggest. Although we did not find strong evidence for a clinically relevant causal effect of allergic disease on mental health (or vice versa), the MR estimates particularly for the allergic disease exposures are precise, enabling us to estimate the maximum causal effect we are likely to see. In addition, investigating both the broad allergic disease phenotype and separating out the specific effects of asthma/AD/hay fever enabled us to determine whether the relationship is driven by certain phenotypes.

There are some limitations to this study that should be considered. First, the available genetic instruments for the mental health phenotypes were weaker than those used for the allergic disease phenotypes (as indicated by R^2 and mF values in Table S10). It is therefore difficult to rule out bidirectional effects that were not uncovered, as it is possible that we did not have enough power to detect causal effects of mental health and personality on allergic disease. Second, although the evidence was strongest for the causal effect of bipolar disorder genetic liability upon hayfever, after accounting for multiple testing using a Bonferroni correction, none of the MR analyses passed the suggested threshold ($p < 1.25 \times 10^{-3}$). However, this approach is likely overly conservative given the correlation between our phenotypes. Third, the UKB phenotypes used within this study were predominantly self-reported, which could increase the potential for misreporting. However, where possible we repeated the observational analysis using a stricter definition of major depression and bipolar disorder, and the results were consistent. Fourth, there was some sample overlap in our MR analyses of neuroticism and both the broad allergic disease and hayfever phenotype, due to the inclusion of UKB in both GWAS. Sample overlap can bias the causal estimate towards the phenotypic exposure-outcome association[31]; however, our MR estimates for these associations were null so this was not an issue. Fifth, the results from this study may not be generalizable across populations. Both the observational data and the publicly available GWAS data used for the MR used data from predominantly white European samples in adulthood. More diverse GWAS are required to improve transferability of results across populations and age groups.[45] Our phenotypic analyses were also performed in a cohort of UK adults recruited when they were in their fourth decade or above, this may limit the generalizability of our findings surrounding disorders that are more prevalent in childhood and adolescence. This is reflected in the lower prevalence rates of allergic disease in our sample compared with the UK population. It is also possible that since cases of allergic disease were self-reported at recruitment, these may reflect more severe phenotypes and/or disease present in UKB adult participants. While our phenotypic analysis is restricted to adults aged 40 years and over, the MR analyses reflect the effect of allergic disease across the life course rather than during a specific developmental period, any effects specific to childhood may therefore be diluted in this sample. Finally, it is important to note that for binary phenotypes MR estimates the effect of genetic liability to a phenotype, not the effect of actually having the phenotype or disease.[30] It is therefore possible the effect of experiencing a specific allergic disease or mental health disorder could have different effects to those reported here.

In conclusion, few of the observed associations between allergic disease and mental health were replicated. The causal effect we did identify appears to be much lower in magnitude than that suggested observationally. This suggests that the majority of co-incidence

observed clinically is unlikely to be causal. Therefore, intervening to prevent onset of allergic disease is unlikely to directly prevent the onset of mental ill-health. But future work should aim to investigate whether interventions that aim to improve allergic disease have a causal effect on mental health (and vice versa).

ACKNOWLEDGEMENTS

This research has been conducted using the UK Biobank Resource under Application Number 10074. Details of patient and public involvement in the UK Biobank are available online (http://www.ukbiobank.ac.uk/about-biobank-uk/ and https://www.ukbiobank.ac.uk/wp-content/uploads/2011/07/Summary-EGF-consultation.pdf). No patients were specifically involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design or implementation of this study. No patients were asked to advise on interpretation or writing up of results. There are no specific plans to disseminate the results of the research to study participants, but the UK Biobank disseminates key findings from projects on its website.

CONFLICT OF INTEREST

LP has received personal fees from Merck for Scientific Input Engagement related to MR methodology. All other authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

AB-A, SJB, LP and HS conceived the study concept. AB-A and HS managed the project. SJ, AB-A and HS performed the statistical analysis. SJ, AB-A, SJB, LP and HS drafted the manuscript. All authors were involved in the interpretation of the data and contributed to and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The UK Biobank dataset used to conduct the research in this paper is available via application directly to the UK Biobank. Applications are assessed for meeting the required criteria for access, including legal and ethics standards. More information regarding data access can be found here: http://www.ukbiobank.ac.uk/scientists-3/. The code and datasets used to carry out the MR analyses are available on GitHub (https://github.com/abudu-aggrey/Allergic_Disease_Mental_Health_MR).

ORCID

Ashley Budu-Aggrey https://orcid.org/0000-0002-8911-2492
Neil M. Davies https://orcid.org/0000-0002-2460-0508
Lavinia Paternoster https://orcid.org/0000-0003-2514-0889
Marcus R. Munafò https://orcid.org/0000-0002-4049-993X
Sara J. Brown https://orcid.org/0000-0002-3232-5251
Jonathan Evans https://orcid.org/0000-0003-3171-640X
Hannah M. Sallis https://orcid.org/0000-0002-4793-6290

REFERENCES

1. Bewley A. The neglected psychological aspects of skin disease. *BMJ*. 2017;358:j3208.
2. Hammer-Helmich L, Linneberg A, Obel C, Thomsen SF, Tang Møllehave L, Glümer C. Mental health associations with eczema, asthma and hay fever in children: a cross-sectional survey. *BMJ Open*. 2016;6(10):e012637.
3. Tzeng NS, Chang HA, Chung CH, et al. Increased risk of psychiatric disorders in allergic diseases: A nationwide, population-based, cohort study. *Front Psychiatry*. 2018;9:133.
4. Pawankar R. Allergic diseases and asthma: A global public health concern and a call to action. *World Allergy Organ J*. 2014;7(1):12.
5. Yaghmaie P, Koudelka CW, Simpson EL. Mental health comorbidity in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2013;131(2):428-433.
6. Wang W-C, Lu M-L, Chen VC-H, et al. Asthma, corticosteroid use and schizophrenia: A nationwide population-based study in Taiwan. Wu P-H, ed. *PLoS One*. 2017;12(3):e0173063.
7. Lin TC, Lee CTC, Lai TJ, et al. Association of asthma and bipolar disorder: A nationwide population-based study in Taiwan. *J Affect Disord*. 2014;168:30-36.
8. Chen YH, Lee HC, Lin HC. Prevalence and risk of atopic disorders among schizophrenia patients: A nationwide population based study. *Schizophr Res*. 2009;108(1–3):191-196.
9. Dunn AJ, Swiergiel AH, De Beaurepaire R. Cytokines as mediators of depression: What can we learn from animal studies? *Neurosci Biobehav Rev*. 2005;29(4–5):891-909.
10. Smith RS. The macrophage theory of depression. *Med Hypotheses*. 1991;35(4):298-306.
11. Martone G. The Inflammation Hypothesis and Mental Illness, vol 2. Pulsus Group; 2019.
12. Köhler-Forsberg O, Sylvia L, Thase M, et al. Nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol do not affect 6-month mood-stabilizing treatment outcome among 482 patients with bipolar disorder. *Depress Anxiety*. 2017;34(3):281-290.
13. Paternoster L, Tilling K, Davey Smith G. Genetic epidemiology and Mendelian randomization for informing disease therapeutics: Conceptual and methodological challenges. *PLoS Genet*. 2017;13(10):e1006944.
14. Lawlor DA, Harbord RM, Sterne JAC, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med*. 2008;27(8):1133-1163.
15. Davey Smith G, Ebrahim S. What can mendelian randomisation tell us about modifiable behavioural and environmental exposures? *BMJ*. 2005;330(7499):1076-1079.
16. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Medicine*. 2015;12(3):e1001779.
17. Smith DJ, Nicholl BI, Cullen B, et al. Prevalence and characteristics of probable major depression and bipolar disorder within uk biobank: cross-sectional study of 172,751 participants. *PLoS One*. 2013;8(11):e75362.
18. Ferreira MA, Vonk JM, Baurecht H, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. *Nat Genetics*. 2017;49(12):1752-1757.
19. Demenais F, Margaritte-Jeannin P, Barnes KC, et al. Multiancestry association study identifies new asthma risk loci that colocalize with immune-cell enhancer marks. *Nat Genet*. 2018;50(1):42-53.
20. Waage J, Standl M, Curtin JA, et al. Genome-wide association and HLA fine-mapping studies identify risk loci and genetic pathways underlying allergic rhinitis. *Nat Genet*. 2018;50(8):1072-1080.
21. Paternoster L, Standl M, Waage J, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. *Nat Genet*. 2015;47(12):1449-1456.
22. Wray NR, Ripke S, Mattheisen M, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet*. 2018;50(5):668-681.

23. Stahl EA, Breen G, Forstner AJ, et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat Genet*. 2019;51(5):793-803.
24. Ripke S, Neale BM, Corvin A, et al. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511(7510):421-427.
25. Luciano M, Hagenaars SP, Davies G, et al. Association analysis in over 329,000 individuals identifies 116 independent variants influencing neuroticism. *Nat Genet*. 2018;50(1):6-11.
26. Otowa T, Hek K, Lee M, et al. Meta-analysis of genome-wide association studies of anxiety disorders. *Mol Psychiatry*. 2016;21(10):1391-1399.
27. Purves KL, Coleman JRI, Meier SM, et al. A major role for common genetic variation in anxiety disorders. *Mol Psychiatry*. 2020;25(12):3292-3303.
28. College Station TSL. StataCorp. 2017; 2017.
29. Hemani G, Zheng J, Elsworth B, et al. The MR-base platform supports systematic causal inference across the human phenome. *Elife*. 2018;7:e34408.
30. Burgess S, Labrecque JA. Mendelian randomization with a binary exposure variable: interpretation and presentation of causal estimates. *Eur J Epidemiol*. 2018;33(10):947-952.
31. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. *Genet Epidemiol*. 2016;40(7):597-608.
32. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genet Epidemiol*. 2016;40(4):304-314.
33. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *Int J Epidemiol*. 2017;46(6):1985-1998.
34. Bowden J, Fabiola Del Greco M, Minelli C, Davey Smith G, Sheehan NA, Thompson JR. Assessing the suitability of summary data for two-sample Mendelian randomization analyses using MR-Egger regression: The role of the I 2 statistic. *Int J Epidemiol*. 2016;45(6):1961-1974.
35. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. Li J, ed. *PLOS Genet*. 2017;13(11):e1007081.
36. Staley JR, Blackshaw J, Kamat MA, et al. PhenoScanner: a database of human genotype-phenotype associations. *Bioinformatics*. 2016;32(20):3207-3209.
37. Kamat MA, Blackshaw JA, Young R, et al. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. *Bioinformatics*. 2019;35(22):4851-4853.
38. Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016;387(10023):1109-1122.
39. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health*. 2012;12(1):204.
40. Pawankar R, Canonica G, Holgate S, Lockey R. *WAO white book on allergy: update 2013*. Pediatriya. Published online 2013.
41. Breuer K, John SM, Finkeldey F, et al. Tertiary individual prevention improves mental health in patients with severe occupational hand eczema. *J Eur Acad Dermatology Venereol*. 2015;29(9):1724-1731.
42. Cork MJ, Eckert L, Simpson EL, et al. Dupilumab improves patient-reported symptoms of atopic dermatitis, symptoms of anxiety and depression, and health-related quality of life in moderate-to-severe atopic dermatitis: analysis of pooled data from the randomized trials SOLO 1 and SOLO 2. *J Dermatol Treat*. 2020;31(6):606-614.
43. All-Party Parliamentary Group on Skin. Mental Health and Skin Disease; 2020.
44. Mahmoud O, Dudbridge F, Davey Smith G, Munafo M, Tilling K. Slope-Hunter: A robust method for index-event bias correction in genome-wide association studies of subsequent traits. *bioRxiv*. 2020:2020.01.31.928077.
45. Mills MC, Rahal C. The GWAS Diversity Monitor tracks diversity by disease in real time. *Nat Genet*. 2020;52(3):242-243.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Budu-Aggrey A, Joyce S, Davies NM, et al. Investigating the causal relationship between allergic disease and mental health. *Clin Exp Allergy*. 2021;00:1–10. https://doi.org/10.1111/cea.14010